REMARKS

Claims 31, 33-38, 40, and 44-46 are pending.

As a preliminary matter, Applicant respectfully requests that the Attorney Docket No. be changed to 8449-153, to reflect the Attorney Docket No. recited on the Revocation and Power of Attorney filed on August 7, 2002, and on the newly submitted Revocation and Power of Attorney filed concurrently herewith.

I. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 31, 33-38, 40, and 44 stand rejected, and new claims 45 and 46 have been rejected, under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Specifically, the Examiner contends that the claims contain subject matter which is not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. In particular, the Examiner contends that (1) administering *Quillaja saponaria* saponins to an individual to treat cancer is unpredictable; (2) the success of using a single agent such as a *Quillaja saponaria* saponin for the treatment of any type of cancer is unpredictable; and (3) administering any type of *Quillaja saponaria* saponin, in either modified or unmodified forms, to treat cancer is unpredictable. Applicant respectfully disagrees, and submits that the claims are fully enabled by the specification as described in detail below.

The legal standard for enablement was presented in Applicant's Amendment Under 37 C.F.R. § 1.114, filed on December 30, 2003.

A. The Claims Are Fully Enabled By The Instant Specification

In light of the legal standard, Applicant submits that the claims are enabled by the instant specification. The instant application provides sufficient teaching to enable one of skill in the art to make and use the methods of the invention which involve administering a composition comprising a *Quillaja saponaria* saponin to treat cancer, without undue experimentation, as described below.

1. *Quillaja saponaria* saponins are effective in treating cancer

The Examiner states that the state of the art at the time of filing teaches that *Quillaja saponaria* saponins can potentiate the innate immune response and are useful as vaccine adjuvants. The Examiner alleges that there is no report that *Quillaja saponaria* saponins have anti-tumor activity. The Examiner concludes that it is unpredictable whether administering *Quillaja saponaria* saponin to an individual can treat cancer because a nexus

between increasing the innate immune response and treating cancer is missing. Applicant respectfully disagrees with the Examiner's rejection.

The Kensil Declaration filed December 30, 2003, previously considered by the Examiner, provides *in vivo* data that supports the efficacy of the use of *Quillaja saponaria* saponins for treatment of cancer. As described therein, a substantially purified saponin, QS-21, inhibited tumor growth in Meth A fibrosarcoma mouse model and in a P815 mastocytoma mouse model. Despite this *in vivo* data, the Examiner contends that a xenograft[1] model for testing anticancer drugs does not make it predictable that QS-21 would be effective in humans. As support, the Examiner cites Gura (1997, Science 278:1041-1042 ("Gura")) as teaching that animal systems for identifying new drugs are often faulty, especially xenograft models.

Gura discusses the limitations of systems of identifying new drugs indicating that of the thousands of drugs shown to have activity in cell or animal models, only 39 have won approval from the U.S. Food and Drug Administration for chemotherapy. *See* Gura at 1041. This argument is similar to the one made by the U.S. Patent and Trademark Office ("PTO") in *In re Brana*, where the PTO argued that similar references, which were cited by the Board of Patent Appeals and Interferences, prove that *in vivo* tests used by the applicants were inadequate to convince one of ordinary skill in the art that the claimed compounds are useful as antitumor agents. *See In re Brana*, 51 F.3d 1560, 1565, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). The Federal Circuit held that the references cited by the Board "do not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of *in vivo* murine tests." *Id.* at 1566. Thus, the Federal Circuit held that the PTO did not meet its initial burden of challenging a presumptively correct assertion of utility[2] in the disclosure. *See id.* Like the references cited in *In re Brana*, Gura only discusses the therapeutic predictive value of *in vivo* murine tests. Accordingly, Applicant submits that the Examiner's evidence does not cause reasonable doubt as to the asserted utility, *i.e.*, treatment of cancer, and that the claims meet the requirements of 35 U.S.C. § 112, first paragraph.

Moreover, as discussed above, the Kensil Declaration provides experimental results demonstrating that QS-21 has antitumor activity in two different standard tumor

[1] Applicant notes that the models described in the Declaration are allografts, not xenografts.

[2] Applicant notes that in *In re Brana*, the Examiner's rejection was based on 35 U.S.C. § 112, first paragraph.

models. In *In re Brana*, similarly, the applicants provided in a declaration test results showing that several compounds exhibited antitumor activity against a standard *in vivo* tumor model. *See id.* at 1567. The PTO argued that *in vivo* tests in animals are not reasonably predictive of the success of the compounds for treating cancer in humans. *See* id. In response, the Federal Circuit countered that the PTO "confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *Id.* The Federal Circuit further stated that "proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility." *Id.*

There are numerous examples in the art of the use of P815 and Meth A tumor models (*i.e.*, the models described in the Kensil Declaration) in preclinical drug development demonstrating that these are standard experimental animal models. *See, e.g.*, Kimura *et al.*, 1999, Eur J Immunol 29:1532-42 (reference **C04** of record); Mescher *et al.* 1996, J Immunother Emphasis Tumor Immunol 19:102-112 (reference **C05** of record); Nakagawa *et al.*, 1998, Semin Thromb Hemost. 24:207-210 (reference **C06** of record); and Rakmilevich *et al.*, 1996, Proc. Natl. Acad. Sci. USA 93:6291-6296 (reference **C07** of record), especially the abstract. Moreover, an entire chapter of the 2001 edition of Current Protocols in Immunology, a standard laboratory manual, is devoted to the use of the P815 Mastocytoma Tumor Model. *See* Gajewski *et al.*, in Current Protocols in Immunology (2001) 20.4.1-20.4.18 ("Gajewski," reference **C02** of record). While this reference was published months after the filing date of the present application, all of the cited references in this chapter have an earlier filing date than the present application. Gajewski states that P815 is commonly used as an experimental tumor model. *See id.* at 20.4.1. Gajewski also states that it has served as a useful tumor model of studies of anti-tumor immunity in vivo. *See id.* at 20.4.16. Thus, Applicants submit that the *in vivo* mouse tumor studies presented in the Kensil Declaration demonstrate that the claims meet the requirements of 35 U.S.C. § 112, first paragraph.

Thus, Applicant reiterates her position that these results directly support the teachings of the specification by showing that QS-21, which is effective in stimulating innate immune response, is effective in treating cancer.

2. <u>*Quillaja saponaria* saponins can be used for the treatment of a wide variety of cancers</u>

The Examiner alleges that the prior art regards the success of using a single agent, such as a composition comprising a *Quillaja saponaria* saponin, for the treatment of

any type of cancer, as unpredictable. As support, the Examiner cites Lynch et al. (2002, Hematology Oncology Clin N Amer 16:775-810; "Lynch") which teaches that carcinogenesis is a step-wise process caused by the accumulation of multiple somatic mutations and Leon (2002, Digest Liver Disease 34:59-63; "Leon") which teaches that several factors are involved in most human malignancies making it difficult to find a single causative agent fully responsible for the disease. Applicant respectfully disagrees.

Lynch and Leon teach that multiple factors are responsible for causing cancer. The statement that it may be difficult to find a single causative agent fully responsible for cancer does not correlate with the ability of a single agent to treat cancer. Thus, the evidence the Examiner has submitted is not dispositive on this issue.

As discussed above, the Kensil Declaration demonstrates the utility of QS-21 to treat cancer in a fibrosarcoma (tumor of fibrous tissue, *i.e.*, tendons and ligaments) mouse model and a mastocytoma (mast cell tumor) mouse model. Results with these two different types of solid tumors would lead one of ordinary skill in the art to conclude that *Quillaja saponaria* saponins can be used to treat a wide variety of cancers.

Thus, the specification and the knowledge of one of ordinary skill in the art would make predictable the use of *Quillaja saponaria* saponins for the treatment of a wide variety of cancers.

3. *Quillaja saponaria* saponins share a common structure which makes the use of modified or unmodified forms of *Quillaja saponaria* saponins to treat cancer predictable

The Examiner alleges that the prior art teaches that the different chemical structures of saponins affect their biological activity. As support, the Examiner cites Rao and Sung (1995, J. Nutr. 125:717S-724S; "Rao") as teaching that the different structures of saponins affect their biological activity. Applicant respectfully disagrees.

As discussed in the Second Declaration of Dr. Charlotte Kensil, *Quillaja saponaria* saponins share a common structure that gives rise to the common innate immunity function, and thus would be expected to function in the same manner with respect to increasing innate immunity and treating cancer. *See* Second Kensil Declaration, ¶ 4. For example, the *Quillaja saponaria* saponins, QS-7, QS-17, QS-18, and QS-21 are all structurally very similar. *See id.* Compared to the large portion of the structure that is identical, any differences between QS-7, QS-17, QS-18, and QS-21 are minor. Moreover, all known *Quillaja saponaria* saponins share two structural features - a triterpene backbone and a 2,3, glucuronic acid carboxyl group - and are acylated. *See id.* at ¶¶ 5 and 7. There are

specific structural components (of *Quillaja saponaria* saponins) that influence innate immunity and immune adjuvant activity. Furthermore, *Quillaja saponaria* saponins have been found to act similarly in innate immunity. *See id.* at ¶ 8. For example, a characteristic shared in common by saponins QS-7, QS-17, QS-18, and QS-21 in regard to enhancement of adaptive immunity is their ability to stimulate IgG2a responses in mice (*see* Kensil *et al.*, 1991, J Immunol 146: 431-437). *See* Second Kensil Declaration, ¶ 8. Despite structural differences between QS-7 and QS-21, QS-7 and QS-21 both stimulate innate immune responses, for example, by enhancing natural killer cell lytic activity (*see* the specification, Figure 3). *See id.* Activated natural killer cells also produce the cytokine interferon gamma (*see* Abbas *et al.*, in Cellular and Molecular Immunology, WB Saunders Company, Philadelphia, PA, 1997, p. 269, reference **C01** of record). *See id.* Snapper and Paul show that interferon gamma stimulates the expression of IgG2a in mice (*see* Snapper *et al.*, 1987, Science 236: 944-947, reference **C09** of record). *See id.* Hence, a characteristic effect on adaptive immunity (enhanced IgG2a response) seen within the class of saponins encompassed by QS-7, QS-17, QS-18, and QS-21 was also seen for QS-7 and QS-21 for the activation of a cell type (natural killer cells) that produce the cytokine (interferon gamma) that mediates that characteristic adaptive immunity effect. *See id.* Hence, the ability of QS-17 and QS-18 to induce an IgG2a response also indicates that these saponins influence the activation of natural killer cells resulting in induction of interferon gamma by the innate immune system. *See id.* Because of the structural similarity of the *Quillaja saponaria* saponins and the correlation of structure with function, one of ordinary skill in the art would conclude that usefulness in innate immunity and treating cancer is reasonably expected to be a general property of the genus of *Quillaja saponaria* saponins. *See id.*

The Examiner contends that it is unpredictable whether any *Quillaja saponaria* saponin, modified or unmodified, can treat cancer, citing Rao as teaching that the different structures of saponins affect their biological activity. While Rao does indicate that the structure of saponin can affect its biological activity, the Examiner's statement disregards the evidence of Kensil IV (Kensil *et al.*, 1991, J. Immunol. 146:431) demonstrating that all four *Quillaja saponaria* saponins, *i.e.*, QS-7, -17, -18, and -21, induced similar antibody IgG2 and IgG2a titers. *See* Second Kensil Declaration at ¶ 11.

Moreover, the teachings of the prior art provide guidance in terms of what kinds of modifications can be made to *Quillaja saponaria* saponins without adversely affecting their immune adjuvant activity. In particular, Soltysik teaches that derivatives of QS-21 containing a modification of a carboxyl group on glucuronic acid induced antibody

titers at levels similar to QS-21. Moreover, IgG2a levels increased according to the same dose response curves as for total IgG. *See* Soltysik, abstract and page 1407. Thus, these kinds of modified *Quillaja saponaria* saponins would be predicted to be effective in treating cancer. *See* Second Kensil Declaration at ¶ 12.

Thus, while different structures of saponins can result in different activities, the shared structure of the *Quillaja saponaria* saponins and similar immunologic activity would lead one of ordinary skill in the art to conclude that the genus of *Quillaja saponaria* saponins would be useful for treating cancer. *See* id. at ¶¶ 4-9.

In conclusion, the specification, knowledge of one of ordinary skill in the art, the experiments presented in the Kensil Declaration, and the teachings of the Second Kensil Declaration demonstrate that one of skill in the art can readily follow the teachings of the specification to use *Quillaja saponaria* saponin to stimulate innate immunity, and thereby treat cancer, without the need for undue experimentation. Accordingly, for the reasons presented above, Applicant asserts that the claimed methods are enabled. Thus, the rejection under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement should be withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks made herein be entered into the record of the instant application. Claims 31, 33-38, 40 and 44 fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejections and early allowance and action for issuance are respectfully requested.

Applicant respectfully requests that the Examiner call the undersigned attorney at (212) 326-3939 if any questions or issues remain.

Respectfully submitted,

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Enclosures